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In re Application of
Masahiko DOHI, et al.
Serial No.: 09/125,814
Berman
Filed: August 26, 1998
For: POWDERY COMPOSITION FOR NASAL ADMINISTRATION

Group Art Unit : 1615
Examiner : Alysia

DECLARATION UNDER 37 C.F.R. 1.132

Hon. Commissioner of Patents and Trademarks,
Washington, D.C. 20231

Sir:

I, Masahiko Dohi, c/o TEIJIN LIMITED, DDS Research Laboratories, 4-3-2 Asahigaoka, Hino, Tokyo191-8512, Japan, do hereby declare:

That I am by profession a research scientist having earned a Master's degree in pharmaceutics from Science University of Tokyo in March 1990;

That I have been employed by TEIJIN LIMITED, Tokyo, Japan, since March 1990;

That I have been engaged in research into the development of pharmaceutical products in the same company to date;

That I am a co-inventor of the invention disclosed and claimed in the above-identified U.S. application (hereinafter referred to as "present invention" for brevity) and hence I am fully familiar therewith;

That I have read and am fully familiar with U.S. Patent 4,613,500 (herein after

"USP 4,613,500") cited against claims of the above-identified U.S. application;

That I personally conducted or supervised the conduct of all of the work reported in the examples including the comparative example in the specification of the present application, and the results obtained are as set forth therein; and

That I carried out the following experimentation to show the differences between the present invention and USP 4,613,500, and to explain the differences between the present invention and USP 4,613,500.

Hereinafter, the abbreviations MCC and HPC represent water-absorbing and water-insoluble base and water-absorbing and water-soluble base, respectively, in USP 4,613,500 and water-absorbing and water-insoluble base and water-absorbing and gel-forming base, respectively, in the present invention.

In order to explain the difference between USP 4,613,500 and the present invention, I compared the following two embodiments in the following table.

	USP 4,613,500		**The Present Invention**
Objective	absorption of drugs efficiently		enhancement of absorption
Make-up of Composition	drug + MCC	drug + MCC + HPC	drug + MCC + HPC
Distribution of drugs	independently, adhered to surface of MCC, dispersed in MCC, or closely dispersed in MCC	independently, adhered to surface of both MCC and HPC, dispersed in both MCC and HPC, or closely dispersed in both MCC and HPC	unevenly distributed on MCC
Role of HPC	without HPC	prolonging plasma profiles produced by drug + MCC formulation	improving plasma profiles; higher maximum concentration and amount of absorption, compared to drug + MCC formulation

Effect	absorption of drugs efficiently compared to ordinary methods, such as solution	prolonging plasma profiles produced by drug + MCC formulation	enhancing absorption; higher maximum concentration and amount of absorption, compared to drug + MCC formulation
Manufacturing Methods		1. simple mixing of HPC, MCC, and drug simultaneously 2. dissolved HPC with drug and freeze-dried and then mixed with MCC	1. strongly mixed MCC with drug, and then with HPC or small particle size of HPC 2. dispersed in MCC with drug and freeze-dried and then mixed with HPC

USP 4,613,500 is directed to achieving a high amount of drug absorption nasally dosed by powder preparation. The present invention is directed to attaining a larger amount of drug absorption. The present invention is composed of MCC, HPC and drugs. In contrast, USP 4,613,500 is basically composed of MCC and drugs, and discloses the joint use of HPC .

These inventions are substantially different. The different points are: 1) distribution of drugs, 2) objective of the addition of HPC and 3) the manufacturing methods. These differences bring out different effects on nasal absorption. In USP 4,613,500, HPC plays a roll to prolong plasma profile resulting from drug + MCC formulation. On the other hand, in the present invention, HPC works for enhancing absorption, such as higher Cmax and higher amount of drug absorption compared to the drug + MCC formulation. This difference is suggested by the following 4 descriptions in USP 4,613,500.

a) The sentence in Column 1, Line 55 - Column 2, Line 2 shows that HPC, lower alkyl ether of cellulose, works to slowly flow on the nasal mucosa and to release

the drug slowly.

b) The sentence in Column 2, Line 23 – Line 27: *It is yet another object of this invention to provide a powdery pharmaceutical composition for nasal administration which allows physiologically active polypeptide or its derivative to be absorbed efficiently through the nasal mucosa and also has* ***a sustained release effect.***

c) The sentence in Column 4, Line 56- Line 66: *When the pharmaceutical composition is intranasally administered, the particles which comprise a water-absorbing and water-insoluble base and polypeptide or its derivative are dispersed over the nasal mucous membrane, and the water-absorbing and water-soluble base is dissolved into the state of a viscous fluid, which gives some degree of viscosity and flowage to the whole base of this invention,* ***thus allowing the polypeptide or its derivative to be absorbed slowly which is known as a sustained release effect.***

d) The sentence in Column 5, Line 3: *In case where the water-absorbing and water-soluble base is freeze-dried together with the polypeptide or its derivative, the mixture assumes the state in which particles of the polypeptide or its derivatives are dispersed among particles of water-absorbing and water-soluble base and* ***the final product of pharmaceutical composition comes to have much more sustained release effect.***

Consequently in USP 4,613,500, the addition of HPC caused prolonging plasma profiles by drug + MCC formulation. On the other hand, the present invention, drug + MCC + HPC formulation, shows higher absorption than the drug + MCC formulation. The present invention attains higher amount of drug absorption and higher maximum plasma concentration (Cmax), but the MCC formulation with

HPC disclosed in USP 4,613,500 did not attain a higher Cmax than the MCC formulation without HPC.

"Cmax" means maximum plasma concentration that is the highest plasma concentration value after dosing. The amount of "drug absorption" means the value of the amount of drug absorbed into the blood after dosing. For example, the value is shown as an area under a plasma concentration - time curve ("AUC"). Therefore, the Cmax is the value at a point, and the amount of drug absorption is a value calculated by the area of its plasma profile.

Accordingly, the correlation between Cmax and the amount of drug absorption is not always fixed. For example, when the plasma profile is sharp (drastically going up and drastically disappearing), Cmax may be high and the amount of drug absorption may be low.

The above differences also are explained by considering the difference of how HPC is added.

In USP 4,613,500, two ways of how to add HPC are described. One is mixing with MCC and ingredients simultaneously, and another is to dissolve HPC with ingredients and then the composition is freeze-dried. These methods to add HPC shows that USP 4,613,500 doesn't suggest the " uneven" distribution of the present invention because these methods definitely distribute ingredients to HPC more than the present invention does. The descriptions regarding how to add HPC are as follows.

Mixing with MCC and ingredient

a) The sentence in Column 4, Line 67 – Column 5, Line 2: *The water-absorbing and water-soluble base may be used* ***by simply mixing it with water-absorbing and water-insoluble base*** *or by mixing it with the polypeptide or its derivative at the time of their freeze-drying.*

b) The sentence in Column 6, Line 38- Line 46: *In case where a water-absorbing and water-soluble base is to be used jointly,* ***it may be admixed with polypeptide or its derivative and a water-absorbing and water-insoluble base in the mechanical mixing process,*** *followed by the above-mentioned process of compacting, etc., or a water-absorbing and water-soluble base may be introduced into the process wherein the polypeptide or its derivative is mixed with a water-absorbing and water-insoluble base in the presence of water.*

Dissolved with ingredients in aqueous solution and then freeze-dried

a) The sentence in Column 4, Line 67 – Column 5, Line 2: *The water-absorbing and water-soluble base may be used by simply mixing it with water-absorbing and water-insoluble base or* ***by mixing it with the polypeptide or its derivative at the time of their freeze-drying.***

b) The sentence in Column 6, Line 47- Line 53: *There is also another method of obtaining a powdery composition by joint use of a water-absorbing and water-soluble base, wherein* ***a water-absorbing and water-soluble base is added to polypeptide or its derivative in the process in which polypeptide or its derivative is to be freeze-dried,*** *thus both components being freeze-dried simultaneously as mentioned above.*

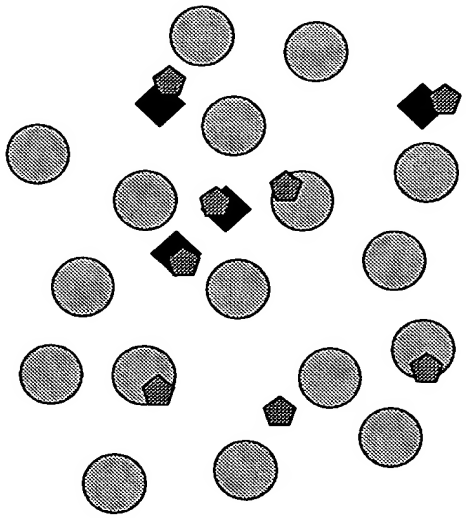
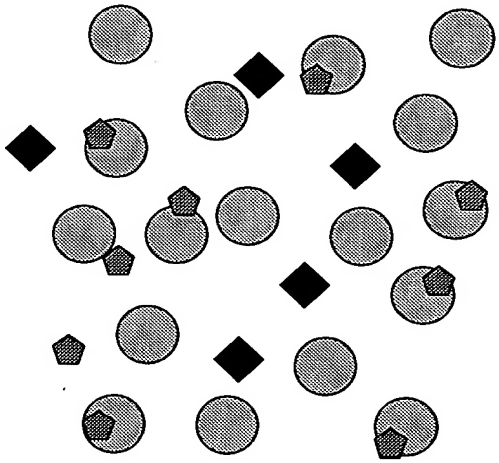
Furthermore these two difference points are suggested from the examples of USP 4,613,500.

In EXAMPLE 2, Fig.1 shows that in the case where freeze-dried insulin-sodium and polyacrylate was used, instead of enhanced absorption effect, sustained release effect was attained compared to the case where crystalline cellulose was used. The example shows that the objective of USP 4,613,500 is just sustained release.

Although they show 3 examples (Examples 1(b), 12, and 13) for cases jointly using HPC, in all 3 examples HPC is added to be dissolved with the ingredients. These examples show that USP 4,613,500 does not teach or suggest the "uneven distribution" of the present invention.

To further show the difference between USP 4,613,5000 and our invention, I illustrated the difference of (a) the distribution of drugs and (b) the effect on plasma profiles as follows.

The Distribution of Drugs

The State of Example 1(b) of US 4,613,500	The state of present invention
	

shows MCC

shows HPC

shows drug

The distribution of drugs is significantly different between the present invention and USP 4,613,500.

The method used to prepare the composition of Example 1(b) of USP 4,613,500 is disclosed at col. 7, lines 28-45. USP 4,613,500 discloses that a composition comprising insulin as a drug, polyacrylic acid as a water- absorbing and water-soluble base material and crystalline cellulose as a water-absorbing and water-insoluble base material is made in the following manner.

Firstly, polyacrylic acid was dissolved in an aqueous solution of insulin.

Secondly, the solution was then freeze-dried to give a powdery composition. Then, the obtained powdery composition and microcrystalline cellulose were put in a mortar and mixed thoroughly to obtain a powdery composition.

Accordingly, most of the drug of the powdery composition obtained by the above mentioned method is dispersed on or in polyacrylic acid (a water- absorbing and water-soluble base material), as shown in the Table above.

The Effect on Plasma Profiles

In Example 2 of US 4,613,500, the respective powdery compositions of insulin prepared in Example 1 were administered intranasally to male Beagle dogs, and the glucose level of plasma was measured by o-toluidine. Fig. 1 of US 4,613,500 shows the decrease (%) of the plasma glucose levels from the levels before administration of insulin. *See* col. 8, lines 5-40.

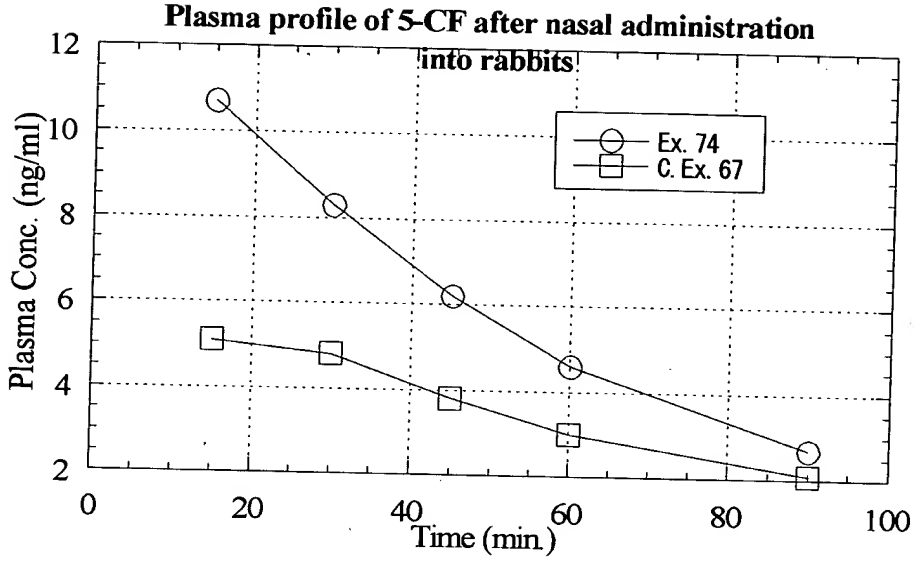
In the present invention, however, there is no data measured by the decrease of the plasma levels from the levels before administration of drug.

Therefore, to compare the effect of US 4,613,500 and the present invention under the same conditions, I adopted the data of Example 74 of the present application as a representative composition of the present invention and the data of Comparative Example 67 of the present application as a representative composition of US 4,613,500, because the method of making the composition of Comparative Example 67 is the same as that of Example 1(b) of US 4,613,500.

Graph 1 shows the plasma profile of 5-CF after nasal administration into rabbits measured in Example 74 and Comparative Example 67 of the present

invention.

Graph 1



The plasma profiles are clearly different between the present invention and USP 4,613,500.

In addition, I have shown the Cmax and AUC calculated by the data of Example 74 and Comparative Example 67 in the Table below.

	Cmax (ng/mL)	AUC (ng/mL*min)
Example 74	10.7	522.0
Comparative Example 67	5.1	304.5

Cmax of Example 74 is 10.7 ng/mL and that of Comparative Example 67 is 5.1ng/mL. It is clear that Cmax of Example 74 is much higher than that of Comparative Example 67.

AUC of Example 74 is 522.0 ng/mL*min and that of Comparative Example 67 is 304.5 ng/mL*min. Clearly, AUC of Example 74 is much larger than that of Comparative Example 67.

In view of the above, I conclude that the present invention is different from the composition of USP 4,613,500 and provides unexpectedly superior results with respect to enhancing drug absorption and maximum plasma concentration.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 12 day of March ,2001

Masahiko Dohi

Masahiko Dohi